REMARKS

Claims 24-29 are pending in this application and are presented for examination. Claims 24 and 25 have been amended. No new matter has been introduced with the foregoing amendment. Reconsideration is respectfully requested.

I. FORMALITIES

Claims 24 and 25 have been amended to remove "5,5-Dithiobis(2-Nitrobenzoic Acid)" (DTNB) from the list of compounds that can be used to inactivate a retrovirus as described in the present invention. Support for amended claims 24 and 25 is found, for example, in Figure 15, panel A, wherein it is shown that DTNB does not disrupt zinc fingers in intact retroviruses, and in Figure 15, panel B, wherein it is shown that DTNB does not inactivate mature, infectious retroviruses. Thus, no new matter has been introduced. As such, Applicants respectfully request that the amended claims be entered.

II. SPECIFICATION OBJECTION

The specification was objected to under 35 U.S.C. § 132 as allegedly containing new matter. In particular, the Examiner states that "the contents of the prior applications 'incorporated herein by reference for all purposes' constitutes new matter because incorporation of these documents was not present at the time the instant application was filed." However, in the transmittal form for the application as originally filed, Applicants requested amending the specification both to claim the benefit of priority and to incorporate by reference U.S. Application Nos. 08/379,420 and 08/312/331. For the convenience of the Examiner, a copy of the application transmittal form is attached hereto as Exhibit 1. Therefore, Applicants respectfully request that the objection be withdrawn.

III. CLAIM OBJECTION

In the Office Action, the Examiner indicated that claim 25 was objected to because "Disulfideformamidine" was presumably two words. Applicants have amended claim 25 by deleting "formamidine disulfide dihydrochloride," thus correcting the informality of "Disulfideformamidine" and eliminating the repetition of said compound in the claim. As such, Applicants respectfully request that the objection be withdrawn.

IV. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 24-29 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

The Examiner alleges that "the metes and bounds of 'derivatives containing the NO group' cannot be determined," as this genus has not been described with sufficient clarity in the specification. In order to expedite prosecution of the present case, Applicants have amended claim 24 to delete "derivatives containing the NO group." In view of the amendment to claim 24, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 112, second paragraph rejection.

V. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

A. New Matter Rejection

Claims 24-29 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the Applicants, at the time the application was filed, had possession of the claimed invention. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

The Examiner alleges that C-nitroso compounds having the formula R-C-NO are considered derivatives containing the NO group, but that "the added phrase constitutes new matter." In order to expedite prosecution, Applicants have amended claim 24 to delete the proviso that the compound is not "a C -nitroso compound of the formula R-C-NO." In view of the amendment to claim 24, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 112, first paragraph rejection.

B. Written Description Rejection

In addition, the Examiner rejected claims 24-29 under 35 U.S.C. § 112, first paragraph, alleging that the specification fails to provide adequate written description of the genus "derivatives containing the NO group," as "the metes and bounds for what would be considered a 'derivative' cannot be determined." As previously explained, in order to expedite prosecution, Applicants have amended claim 24 to delete "derivatives containing the NO group" from the claim. In view of the amendment to claim 24, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 112, first paragraph rejection.

VI. REJECTION UNDER 35 U.S.C. § 102(b): Rice *et al.*

Claims 24, 28, and 29 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Rice *et al.* In particular, the Examiner alleges that "Rice *et al.* inactivate HIV with C-nitroso compounds" and that "exclusion of these compounds from the claims represents new matter." Continuing, the Examiner alleges that C-nitroso compounds" are also considered 'derivatives containing the NO group.'" Therefore, the Examiner concludes that the teachings of Rice *et al.* anticipate the present invention. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

Applicants have amended claim 24 to delete the proviso that the compound is not "a C -nitroso compound of the formula R-C-NO." Further, Applicants have amended claim 24 to delete "derivatives containing the NO group" from the claim.

As such, each and every element as set forth in amended claim 24 is not found in the Rice *et al.* reference, and the compounds claimed in amended claim 24 would therefore not be anticipated by the teachings of Rice *et al.* In view of the foregoing, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 102(b) rejection.

VII. REJECTION UNDER 35 U.S.C. § 102(a)/103(a): Ryser *et al.*

Claims 24-26, 28, and 29 were rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by, or, in the alternative, under 35 U.S.C. § 103(a) as allegedly being obvious over Ryser *et al.* The Examiner alleges that "Ryser *et al.* anticipate an inactivated retrovirus that has been inactivated with 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB)." Further, the Examiner alleges that "since the compound is a disulfide and inactivates HIV, the teachings of Ryser *et al.* anticipate each element in the claims." Therefore, the Examiner concludes that Applicants' inactivated retrovirus "reasonably appears to encompass disrupted zinc fingers that are indistinguishable from the reference's inactivated retrovirus." To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

Applicants submit herewith a Declaration of Dr. Louis E. Henderson under 37 C.F.R. § 1.132 ("the Declaration"). As explained by Dr. Henderson in the Declaration, Ryser *et al.* teach that DTNB, a membrane-impermeant sulfhydryl reagent, inhibits HIV infection by inhibiting the non-zinc finger-containing protein disulfide-isomerase (PDI) on the surface of the host cell. Because DTNB is membrane-impermeant, it cannot cross the viral envelope to reach and disrupt zinc finger-containing nucleocapsid proteins. Therefore, DTNB <u>does not inactivate</u> the mature, infectious HIV virus.

As such, contrary to the Examiner's allegation, Ryser *et al.* do not teach an inactivated retrovirus, as DTNB inhibits the PDI protein on the surface of the host cell, and does not in any way act directly on the mature, infectious retrovirus. By contrast, the present invention teaches a mature retrovirus inactivated by means of <u>direct disruption</u> of one or more CCHC zinc fingers in the viral nucleocapsid proteins. As such, Applicants

believe that each and every element in the claims of the present invention is not found in the Ryser *et al.* reference. In view of the foregoing, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 102(a) rejection.

Alternatively, claims 24-26, 28, and 29 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Ryser *et al.* In response, Applicants respectfully traverse the rejection.

As set forth in M.P.E.P. § 2143:

> [t]o establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure.

I*n re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

All three elements set forth above must be present in order to establish a *prima facie* case of obviousness. However, Applicants assert that a *prima facie* case of obviousness has not been established for the following reasons: 1) there is no suggestion or motivation to modify the reference; 2) there is no reasonable expectation of success; and 3) the cited reference does not teach or suggest all the claim limitations.

Applicants assert that there is simply no motivation or suggestion provided in the cited reference to modify its teachings in the way the Examiner has contemplated. Ryser *et al.* teach inhibition of HIV infection using the disulfide compound DTNB to inhibit a host cell surface protein, *i.e.,* PDI. By contrast, the present invention teaches retroviral inactivation using compounds that penetrate the mature viral membrane and directly disrupt one or more CCHC zinc fingers in the viral nucleocapsid proteins. Thus, because Ryser *et al.* specifically use the disulfide compound DTNB to inhibit a host cell

protein, there would have been no suggestion or motivation to modify these teachings and use other compounds to inactivate a retrovirus directly.

Further, Applicants assert that there is absolutely no reasonable expectation that the compositions of the present invention would be successful based on the teachings of Ryser *et al.* In fact, the data presented in Figure 15, panels A and B, of the present application demonstrate that DTNB does not disrupt zinc fingers in intact retroviruses and therefore does not inactivate retroviruses. As such, one of skill in the art would not have expected, at the time of the present invention, that the use of compounds as claimed to inactivate retroviruses would be successful.

Finally, Applicants assert that Ryser *et al.* do not teach or suggest all the limitations of the claims. As discussed above, the present invention teaches a composition comprising a retrovirus inactivated by direct disruption of viral nucleocapsid proteins. Ryser *et al.* do not teach or suggest such compositions. Again, Ryser *et al.* teach inhibition of viral infection by disruption of a protein on the host cell surface. Therefore, the Examiner has failed to present a *prima facie* case of obviousness. As such, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 103(a) rejection.

VIII. REJECTION UNDER 35 U.S.C. § 102(a)/103(a): Williams *et al.*

Claims 24-29 were rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by, or, in the alternative, under 35 U.S.C. § 103(a) as allegedly being obvious over Williams *et al.* The Examiner alleges that the Aldrithiol-2 compound of claim 27 has an identical CAS registry number to the bis(4-chlorophenyl) disulfide compound of Williams *et al.* In addition, the Examiner alleges that "Williams *et al.* claims inactivating HIV reverse transcriptase and infection" using this compound. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

As set forth by Dr. Henderson in the Declaration, Williams *et al.* teach the use of novel indole compounds for inhibiting HIV reverse transcriptase and preventing or treating HIV infection. However, neither Aldrithiol-2 nor bis(4-chlorophenyl) disulfide

is an indole compound. In fact, contrary to the Examiner's allegation, Aldrithiol-2 is clearly a different compound than bis(4-chlorophenyl) disulfide, as shown in Exhibits B and C accompanying the Declaration. Moreover, both compounds are structurally different from the indole compounds disclosed and claimed in Williams *et al.* In fact, as pointed out by Dr. Henderson in the Declaration, the use of Aldrithiol-2 is neither disclosed nor claimed in Williams *et al.*, and bis(4-chlorophenyl) disulfide is ***only*** used in Example 57 on page 109 of the specification as a component of the reaction used to synthesize an indole compound of claim 1. Therefore, Williams *et al.* fail to teach the use of either compound in inhibiting HIV reverse transcriptase or preventing or treating HIV infection.

In contrast to Williams *et al.*, the present invention teaches retroviral inactivation using Aldrithiol-2 to directly disrupt one or more CCHC zinc fingers in the viral nucleocapsid proteins. As such, Applicants believe that each and every element in the claims of the present invention is not found in the Williams *et al.* reference. In view of the foregoing, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 102(a) rejection.

Alternatively, claims 24-29 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Williams *et al.* In response, Applicants respectfully traverse the rejection.

As discussed above, M.P.E.P. § 2143 sets forth three elements that must be present in order to establish a *prima facie* case of obviousness. However, Applicants assert that a *prima facie* case of obviousness has not been established for the following reasons: 1) there is no suggestion or motivation to modify the reference; 2) there is no reasonable expectation of success; and 3) the cited reference does not teach or suggest all the claim limitations.

Applicants assert that there is simply no motivation or suggestion provided in the cited reference to modify its teachings in the way the Examiner has contemplated. Williams *et al.* specifically teach the use of novel indole compounds for inhibiting HIV

reverse transcriptase and preventing or treating HIV infection. However, Williams *et al.* do not teach or suggest the use of compounds claimed in the present invention for retroviral inactivation by means of direct disruption of viral nucleocapsid proteins. As such, there would have been no suggestion or motivation to modify the teachings of Williams *et al.* to arrive at the present invention.

Further, Applicants assert that there is absolutely no reasonable expectation that the compositions of the present invention would be successful based on the teachings of Williams *et al.* Because Williams *et al.* do not disclose or suggest the use of compounds claimed in the present invention for direct viral inactivation, one of skill in the art would not have expected, at the time of the present invention, that the use of such compounds to inactivate retroviruses would be successful.

Finally, Applicants assert that Williams *et al.* do not teach or suggest all the limitations of the claims. As discussed above, the present invention teaches a composition comprising a retrovirus inactivated by direct disruption of viral nucleocapsid proteins using compounds such as disulfides, maleimides, *etc.* Williams *et al.* do not teach or suggest such compositions. Rather, Williams *et al.* teach only the use of indole compounds for inhibiting HIV reverse transcriptase and preventing or treating HIV infection. Therefore, the Examiner has failed to present a *prima facie* case of obviousness. As such, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 103(a) rejection.

IX. REJECTION UNDER 35 U.S.C. § 102(a)/103(a): Levine *et al.* WO 93/15730

Claims 24-26, 28, and 29 were rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by, or, in the alternative, under 35 U.S.C. § 103(a) as allegedly being obvious over Levine *et al.* WO 93/15730. The Examiner alleges that "the method of Levine *et al.* comprising the compound [DTNB] and the HIV with a disabled viral protease anticipates a composition comprising an inactivated retrovirus since the compound inhibits the virus replication." To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

As set forth by Dr. Henderson in the Declaration, Levine *et al.* teach the use of DTNB to inhibit a purified recombinant viral protease. Examples 1 and 2 on pages 14-17 of Levine *et al.* demonstrate inhibition of recombinant HIV protease, and not of a mature, active retrovirus. As a result, Levine *et al.* do not teach inactivation of a mature, infectious retrovirus, but instead teach inhibition of a recombinant viral protease.

Further, as set forth by Dr. Henderson in the Declaration, the viral protease is responsible for cleaving the viral polyprotein into mature viral proteins. The protease is active when an immature viral particle, containing unprocessed polyprotein, buds from the host cell. After the protease cleaves the polyprotein, thereby converting the immature viral particle into a mature infectious viral particle, the protease has completed its function. As such, protease inhibitors in general inhibit the viral protease inside the host cell so that when an immature particle buds from the cell, it remains inactive and never matures into an active retrovirus. As a result, ***the immature viral particle is never activated, thus rendering it incapable of being inactivated.*** Protease inhibitors do not inactivate mature, infectious retroviruses because the function of the protease has already been completed at this point. Therefore, Levine *et al.* teach viral protease inhibition on a recombinant viral protease, but provide no teaching or suggestion on how to inhibit a viral protease in a host cell or a viral particle, as DTNB is membrane-impermeant.

In particular, the present invention teaches a retrovirus inactivated by means of direct disruption of one or more CCHC zinc fingers in the viral nucleocapsid proteins from a mature, active retrovirus. Applicants assert that not only are the proteins targeted by Levine *et al.* and the present invention distinct (viral protease *vs.* nucleocapsid protein), but the compounds of the present invention **act on the mature, active retrovirus**, whereas the DTNB compound of Levine *et al.* **acts on a recombinant viral protease**. As such, Applicants believe that each and every element in the claims of the present invention is not found in the Levine *et al.* reference. In view of the foregoing,

Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 102(a) rejection.

Alternatively, claims 24-26, 28, and 29 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Levine *et al.* In response, Applicants respectfully traverse the rejection.

As discussed above, M.P.E.P. § 2143 sets forth three elements that must be present in order to establish a *prima facie* case of obviousness. However, Applicants assert that a *prima facie* case of obviousness has not been established for the following reasons: 1) there is no suggestion or motivation to modify the reference; 2) there is no reasonable expectation of success; and 3) the cited reference does not teach or suggest all the claim limitations.

Applicants assert that there is simply no motivation or suggestion provided in the cited reference to modify its teachings in the way the Examiner has contemplated. Levine *et al.* specifically teach the use of the membrane-impermeant sulfhydryl DTNB to inhibit a purified recombinant viral protease. By contrast, compounds used for inactivating a mature retrovirus according to the present invention must be able to permeate the viral envelope membrane in order to access the zinc fingers in the viral nucleocapsid proteins. Therefore, there would have been no suggestion or motivation to modify the teachings of Levine *et al.* to arrive at the inactivated retroviruses of the present invention.

Further, Applicants assert that there is absolutely no reasonable expectation that the compositions of the present invention would be successful based on the teachings of Levine *et al.* Because Levine *et al.* teach the use of a membrane-impermeant reagent for inhibiting a recombinant viral protease and do not teach or suggest its use for inactivating mature retroviruses, one of skill in the art would not have expected, at the time of the present invention, that the use of the presently claimed compounds to inactivate mature, infectious retroviruses would be successful.

Finally, Applicants assert that Levine *et al.* do not teach or suggest all the limitations of the claims. As discussed above, the present invention teaches a composition comprising a mature, active retrovirus inactivated by disruption of one or more CCHC zinc fingers in the viral nucleocapsid proteins. Levine *et al.* do not teach or suggest such compositions. Again, Levine *et al.* teach only the use of the disulfide compound DTNB to inhibit a recombinant viral protease. Therefore, the Examiner has failed to present a *prima facie* case of obviousness. As such, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 103(a) rejection.

X. REJECTION UNDER 35 U.S.C. § 102(a)/103(a): Levine *et al.* WO 92/15329

Claims 24, 28, and 29 were rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by, or, in the alternative, under 35 U.S.C. § 103(a) as allegedly being obvious over Levine *et al.* WO 92/15329 ("the '329 Levine *et al.* reference"). The Examiner alleges that the '329 Levine *et al.* reference "anticipates an inactivated retrovirus that has been inactivated with a copper ion delivery agent." To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

As set forth by Dr. Henderson in the Declaration, the '329 Levine *et al.* reference teaches the use of copper agents to inhibit a purified recombinant viral protease. As a result, similar to the above-described Levine *et al.* reference using DTNB, the '329 Levine *et al.* reference does not teach the inactivation of a mature, infectious retrovirus with any compound, but instead teaches inhibition of a recombinant viral protease with copper agents. By contrast, the present invention teaches a composition comprising a mature retrovirus inactivated by means of direct disruption of viral nucleocapsid proteins using compounds such as copper agents. Therefore, contrary to the Examiner's allegation, the '329 Levine *et al.* reference does not anticipate an inactivated retrovirus of the present invention, as inhibition of a recombinant protease is clearly different and distinct from inactivation of a mature retrovirus.

Applicants further assert that not only are the proteins targeted by the '329 Levine *et al.* reference and the present invention distinct (viral protease *vs.* nucleocapsid protein), but the compounds of the present invention **act on the mature, active retrovirus**, whereas the compounds of the '329 Levine *et al.* reference **act on a recombinant viral protease**. As such, Applicants believe that each and every element in the claims of the present invention is not found in the '329 Levine *et al.* reference. In view of the foregoing, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 102(a) rejection.

Alternatively, claims 24, 28, and 29 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over the '329 Levine *et al.* reference. In response, Applicants respectfully traverse the rejection.

As discussed above, M.P.E.P. § 2143 sets forth three elements that must be present in order to establish a *prima facie* case of obviousness. However, Applicants assert that a *prima facie* case of obviousness has not been established for the following reasons: 1) there is no suggestion or motivation to modify the reference; 2) there is no reasonable expectation of success; and 3) the cited reference does not teach or suggest all the claim limitations.

Applicants assert that there is simply no motivation or suggestion provided in the cited reference to modify its teachings in the way the Examiner has contemplated. The '329 Levine *et al.* reference specifically teaches the use of copper agents to inhibit a recombinant viral protease. By contrast, copper agents are used for inactivating a mature, active retrovirus in compositions according to the present invention. As such, Applicants assert that it would not have been obvious to one of skill in the art to modify the teachings of the '329 Levine *et al.* reference directed to recombinant viral protease inhibition using copper agents to viral nucleocapsid protein disruption using copper agents for the following reasons: 1) viral proteases and viral nucleocapsid proteins differ in both domain structure and function; and 2) inhibition of a recombinant viral protease is clearly different and distinct from inactivation of a mature retrovirus. Therefore, in view

of the foregoing, there would have been no suggestion or motivation to modify the teachings of the '329 Levine *et al.* reference to arrive at the inactivated retroviruses of the present invention.

Further, Applicants assert that there is absolutely no reasonable expectation that the compositions of the present invention would be successful based on the teachings of the '329 Levine *et al.* reference. Because the '329 Levine *et al.* reference teaches the use of copper agents for inhibiting a recombinant viral protease and does not teach or suggest their use for disrupting viral nucleocapsid proteins from a mature retrovirus, one of skill in the art would not have expected, at the time of the present invention, that the use of these compounds to inactivate retroviruses would be successful.

Finally, Applicants assert that the '329 Levine *et al.* reference does not teach or suggest all the limitations of the claims. As discussed above, the present invention teaches a composition comprising a mature retrovirus inactivated by direct disruption of viral nucleocapsid proteins using compounds such as copper agents. The '329 Levine *et al.* reference does not teach or suggest such compositions. Rather, the '329 Levine *et al.* reference teaches only the use of copper agents to inhibit a recombinant viral protease and does not teach or suggest their use for direct retroviral inactivation. Therefore, the Examiner has failed to present a *prima facie* case of obviousness. As such, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 103(a) rejection.

XI. DOUBLE PATENTING REJECTION

Claims 24-29 were rejected under the judicially created doctrine of obviousness-type double patenting for allegedly not being patentably distinct over claims 1, 6-9, and 25-28 of U.S. Patent No. 6,001,555. In the Office Action, the Examiner has indicated that the double patenting rejection can be overcome by the filing of a Terminal Disclaimer (*see*, page 12 of the Office Action).

Applicants respectfully request that this obviousness-double patenting rejection be held in abeyance until Applicants receive from the Examiner an indication

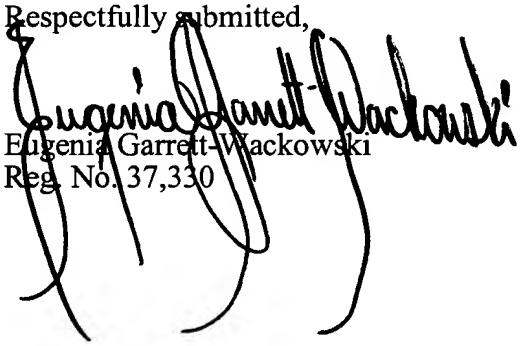
regarding allowable subject matter. At that time, Applicants will file a Terminal Disclaimer as suggested by the Examiner.

XII. CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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Attorney Docket No. 15280-169300US

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Date of Deposit: November 1, 1999

I hereby certify that this is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above, addressed to:

Assistant Commissioner for Patents
Washington, D.C. 20231

By: Marcia C. Jansen

ASSISTANT COMMISSIONER FOR PATENTS
BOX PATENT APPLICATION
Washington, D.C. 20231

Sir:
Transmitted herewith for filing under 37 CFR 1.53(b) is the
[ ] patent application of
[ ] continuation patent application of
[X] divisional patent application of
[ ] continuation-in-part patent application of

Inventor(s)/Applicant Identifier:

For:

[X] This application claims priority from each of the following Application Nos./filing dates: 08/379,420 filed January 27, 1995, which is a continuation-in-part application of USSN 08/312,331, filed September 23, 1994.

[X] Please amend this application by adding the following before the first sentence: "This application is a [X] continuation [ ] continuation-in-part of and claims the benefit of U.S. Continuation in Part (CIP) Application No. 08/379,420 filed January 27, 1995, which is a continuation-in-part application of USSN 08/312,331, filed September 23, 1994, the disclosures of which are incorporated by reference."

Enclosed are:
[X] 40 page(s) of specification
[X] 6 page(s) of claims
[X] 1 page of Abstract
[X] 15 sheet(s) of [ ] formal [X] informal drawing(s).
[X] An assignment of the invention to The United States of America, As Represented by the Secretary of the Department of Health and Human Services,
[X] A [ ] signed [X] unsigned Declaration & Power of Attorney
[ ] A [ ] signed [ ] unsigned Declaration.
[ ] A Power of Attorney by Assignee with Certificate Under 37 CFR Section 3.73(b).
[ ] A verified statement to establish small entity status under 37 CFR 1.9 and 37 CFR 1.27 [ ] is enclosed [ ] was filed in the prior application and small entity status is still proper and desired.
[ ] A certified copy of a _____ application.
[ ] Information Disclosure Statement under 37 CFR 1.97.
[ ] A petition to extend time to respond in the parent application.
[ ] Notification of change of [ ] power of attorney [ ] correspondence address filed in prior application.
[X] Preliminary Amendment

	(Col. 1)	(Col. 2)
FOR:	NO. FILED	NO. EXTRA
BASIC FEE		
TOTAL CLAIMS	23 - 20	= *3
INDEP. CLAIMS	4 - 3	= *1
[ ] MULTIPLE DEPENDENT CLAIM PRESENTED		

* If the difference in Col. 1 is less than 0, enter "0" in Col. 2.

SMALL ENTITY			OTHER THAN SMALL ENTITY	
RATE	FEE	OR	RATE	FEE
	$380.00	OR		$760.00
x $9.00 =		OR	x $18.00 =	$54.00
x $39.00 =		OR	x $78.00 =	$78.00
+ $130.00 =		OR	+ $260.00 =	
TOTAL		OR	TOTAL	$892.00

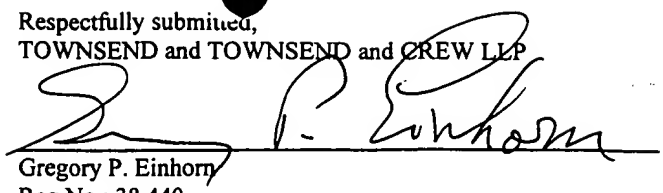
Please charge Deposit Account No. 20-1430 as follows:
[X] Filing fee $ $892.00
[X] Any additional fees associated with this paper or during the pendency of this application.
[ ] The issue fee set in 37 CFR 1.18 at or before mailing of the Notice of Allowance, pursuant to 37 CFR 1.311(b)

EXHIBIT
1

[ ] A check for $_____ is enclosed.

2 extra copies of this sheet are enclosed.

Respectfully submitted,
TOWNSEND and TOWNSEND and CREW LLP



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